Remarks

Claims 1-10 to 14-23 are pending. Claims 10 and 23 have been canceled. Thus, claims 1-9 and 14-22 remain under consideration. Claims 9, 14, and 22 are amended.

Applicants respectfully request reconsideration of the application in view of the claim amendments and the following remarks

Amendments to the Claims

Claim 9 has been amended to recite a method of treating dermal lesions caused by venom-induced-immune dysregulation wherein the site of the lesion comprises a spider bite. The amendment is fully supported by the specification at, for example, page 5, lines 18-26, and original claim 10.

Claim 14 has been amended to recite a method of inhibiting dermonecrosis caused by venom-induced immune dysregulation, the method comprising applying a therapeutically effective amount of an immune response modifier compound to the site of the venom-induced immune dysregulation. This amendment is fully supported by the specification, for example, from page 4, line 27 through page 6, line 18.

Claim 22 has been amended to recite a method of inhibiting dermonecrosis caused by venom-induced immune dysregulation wherein the site of the lesion comprises a spider bite. This amendment is fully supported by the specification at, for example, page 5, lines 18-26, and original claim 23.

§ 103 Rejections

Claims 1-10 and 14-23 stand rejected under 35 USC § 103(a) as being unpatentable over Tomai *et al.* and Gerster *et al.* in view of Bitterman-Deutsch *et al.*, Merigian and Blaho, and Binder. Claims 10 and 23 have been canceled. Thus, the rejection and the following remarks pertain to claims 1-9 and 14-22.

Applicant submits that the present rejection still fails to establish a *prima facie* case of obviousness. § 706.02(j) of the M.P.E.P. states that in order to establish a *prima facie* case of obviousness, three basic criteria must be met:

> (1) there must be some suggestion or motivation in the cited references to modify the references or combine the reference teachings;

(2) there must be a reasonable expectation of success; and

(3) the prior art reference (or references when combined) must teach or suggests all of the claim limitations.

Applicant submits that one of ordinary skill in the art at the time the invention was made would have had no motivation to combine the references as suggested in the Office Action because the collective teachings of the cited references teach away from the suggested combination of references. Furthermore, one of ordinary skill in the art would not have had a reasonable expectation that the recited compounds – compounds known to inhibit eosinophils – could successfully be employed to treat dermal lesions caused by venom-induced immune dysregulation.

Tomai teaches imidazoquinoline amine compounds. Gerster teaches thiazoloquinoline compounds. Tomai and Gerster teach that the compounds described in each reference are useful for treating T_H2-mediated (e.g., IgE-mediated) conditions. The Office Action acknowledges that neither Tomai nor Gerster teaches that the imidazoquinoline amine compounds or the thiazoloquinoline compounds are useful for treating or preventing dermal lesions caused by venom-induced immune dysregulation.

The Office Action cites Bitterman-Deutsch *et al.* as teaching that necrotic cutaneous ulcerations caused by venomous *Loxosceles reclusus* bites may be treated with dapsone because dapsone presumably reduces activity of polymorphonuclear (PMN) leukocytes. The Office Action cites Merigian and Blaho as teaching that *L. reclusus* envenomation leads to accumulation of PMN leukocytes and that the local bite area is often filled with inflammatory infiltration of neutrophils and eosinophils. Finally, the Office Action cites Binder as teaching that *L. reclusus* envenomations can cause cell membrane lysis and chemotaxis (the Office action states that Binder teaches the preceding with respect to black widow spider envenomations, but the subject matter cited from Binder pertains to *L. reclusus* envenomations).

The Office Action states, "employing the imidazoquinoline and thiazoquinoline compounds herein to treat or prevent dermal lesions caused by brown recluse spider or black widow spider envenomation would be reasonably expected to be effective since blocking polymorphonuclear leukocyte activities (for example dapsone) [sic] and chemotaxis is an effective treatment module for the spider envenomation." In responding to Applicant's previous

arguments, the Office Action continues, "the collective teachings of the cited prior art would suggest employing the herein claimed compounds to inhibit esinophils [sic] (polymorphonuclear leukocyte) in order to treat the necrosis."

However, the collective teachings of the cited references *teach away* from using eosinophil inhibiting drugs as treatments for venom-induced dermonecrosis. Therefore, the present rejection is improper and should be withdrawn.

Steroids, generally, and corticosteroids in particular are, like the recited compounds, known to (a) inhibit eosinophils, and (b) are effective for treating eosinophil-mediated (e.g., T_H2-mediated or IgE-mediated) conditions including asthma, allergic rhinitis, eczema, and rheumatoid arthritis. Yet, Wasserman and Anderson state that steroids provide no proven benefit for management of venom-induced dermonecrosis resulting from brown recluse spider bites (Table II, page 463, and page 464, last full paragraph). Merigian and Blaho reach the same conclusion regarding use of corticosteroids: "Corticosteroids have shown no clear benefit in brown recluse spider bites other than systemic loxacialism [dermonecrosis is *not* systemic loxacialism]. Most studies have shown either no effect or lesions that are larger than those that went untreated." (p. 731, final paragraph, and Table 5)

Therefore, contrary to the assertion made in the Office Action, the collective teachings of the cited prior art would not have suggested employing compounds that inhibit eosinophils to treat venom-induced dermonecrosis. The collective teachings of the cited references would, in fact, have *dissuaded* one from using compounds that inhibit eosinophils to treat venom-induced dermonecrosis.

Additionally, the argument that the collective teaching of the cited references that the use of dapsone (a neutrophil inhibitor) to treat venom-induced dermonecrosis would have suggested to one of ordinary skill in the art to treat venom-induced dermonecrosis with a recited compound (eosinophil inhibitors) is based on an incomplete and incorrect understanding of the collective teaching of the cited references.

Applicant acknowledges that the recited compounds are, in Tomai and Gerster, disclosed as being useful for treating T_H2-mediated, or IgE-mediated, conditions by inhibiting eosinophils.

Applicant further acknowledges that eosinophils are polymorphonuclear leukocytes (PMNs). However, eosinophils are but one subset of PMNs and, moreover, constitute a substantial minority of cells in the total PMN population. Consequently, while all while

eosinophils are PMNs, not all PMNs are eosinophils. Therefore, it is improper to construe statements that refer, generally, to PMNs as referring to eosinophils specifically.

Applicants acknowledge that dapsone has been suggested as useful for treating venom-induced dermonecrosis and is known to inhibit neutrophils. However, the efficacy of dapsone treatment for venom-induced dermonecrosis is, in the words of Merigian and Blaho "not well defined. The results from the available reports are informative *but cannot be used to justify dapsone therapy*." (page 728, last full paragraph, emphasis added). Thus, the collective teachings of the cited references regarding the utility of dapsone for treating venom-induced dermonecrosis is contradictory. It is unclear how this contradictory teaching in the art can provide the required motivation to combine the references as suggested in the Office Action.

Moreover, there is no teaching or suggestion anywhere in the cited references that dapsone, like the recited compounds, inhibits eosinophils. As stated above, it is improper to construe statements that refer, generally, to PMNs as referring to eosinophils specifically. Thus, one cannot conclude from the teaching of Bitterman-Deutsch (that dapsone reduces the activity of polymorphonuclear leukocytes - suspect as it is in light of Merigian and Blaho) that dapsone reduces the activity of eosinophils in particular. As Applicant stated in the previous Response, neutrophils are specifically identified in the art as a subpopulation of PMNs inhibited by dapsone (see *Clinical Toxicology Review*). No such teaching that dapsone inhibits eosinophils has been found. Even if, for the sake of argument, dapsone did inhibit eosinophils, the cited art would have dissuaded one of ordinary skill in the art from using an eosinophil inhibiting compound to treat venom-induced dermonecrosis.

Consequently, one of ordinary skill in the art, in light of the collective teachings of the cited art, would not have considered dapsone to be an effective treatment for venom-induced dermonecrosis. Even if, for the sake of argument, one of ordinary skill in the art considered dapsone a possible treatment for venom-induced dermonecrosis, one would not have associated the use of dapsone – a neutrophil inhibitor, but not an eosinophil inhibitor - with the use of the recited compounds – eosinophil inhibitors - for treating venom-induced dermonecrosis. Even if, for the sake of argument, one associated the use of dapsone with the use of an eosinophil inhibitor for treating venom-induced dermonecrosis, the collective teachings of the recited references would have suggested that use of an eosinophil inhibiting compound would be ineffective for treating venom-induced dermonecrosis.

One of ordinary skill in the art would not have been motivated to inhibit eosinophils to treat venom-induced dermonecrosis because (a) the collective teachings of the cited references teach away from using eosinophil inhibiting drugs for the treatment of venom-induced dermonecrosis, and (b) the collective teachings of treating venom-induced dermonecrosis with dapsone are contradictory, and any findings regarding the efficacy of treatment using dapsone (a neutrophil inhibitor) provides no guidance regarding treatment using a recited compound (an eosinophil inhibitor).

The rejection of claims 1-9 and 14-22 under 35 USC § 103(a) as being unpatentable over Tomai *et al.* and Gerster *et al.* in view of Bitterman-Deutsch *et al.*, Merigian and Blaho, and Binder is improper and should be withdrawn.

§ 112 Rejections

Claims 1-10 stand rejected under 35 USC § 112, first paragraph, as failing to reasonably provide enablement for the full scope of the claims. Claim 10 has been canceled. Accordingly, the rejection and the following remarks pertain to claims 1-9.

While the Office Action acknowledges enablement for the compounds disclosed in the patent documents cited in Applicants' specification from page 3, line 32 to page 4, line 4, the Office Action asserts that the specification fails to provide information that would allow the skilled artisan to practice the full scope of the claimed invention without undue experimentation. Specifically, the Office Action asserts that the instant claims read on **all** (emphasis in Office Action) compounds in the recited chemical classes, necessitating an exhaustive search for embodiments suitable to practice the claimed invention.

Applicant respectfully disagrees with the position stated in the Office Action. Applicant submits that the scope of the compounds recited in the claims is commensurate with the scope of compounds disclosed in the recited patent documents – those for which enablement has been acknowledged. Contrary to the assertion in the Office Action, claims 1-9 do not read on using all compounds in the recited chemical classes for treating dermal lesions caused by venom-induced immune dysregulation. The compounds disclosed in the recited patent documents are described on the basis of chemical structure *and* biological activity (e.g., antiviral and/or antitumor activity). The method includes applying to a lesion site a therapeutically effective amount of an immune response modifier compound – defined, in Applicant's disclosure (page 2, line 5), as

possessing antiviral or antitumor activity. The compounds recited in the claims, therefore, are compounds within the scope of one of the recited patent documents, enablement for which are acknowledged in the Office Action.

In summary, Applicant submits that claims 1-9 do not purport to cover compounds other than those for which enablement has been acknowledged. Claims 1-9 therefore satisfy the requirements of 35 USC § 112, first paragraph, and that the rejection should be withdrawn.

Claims 14-23 stand rejected under 35 USC § 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to make and/or use the invention. Claim 23 has been canceled. Accordingly, the rejection and the following remarks pertain to claims 14-22.

The Office Action objects to use of the term "preventing" in the claim, even given Applicant's clarification of the meaning of "preventing" in Applicant's prior response. Applicant has amended claim 14 to recite a method of inhibiting dermonecrosis caused by venom-induced immune dysregulation, in order to expedite prosecution. Withdrawal of the rejection of claims 14-22 under 35 USC § 112, first paragraph, is respectfully requested.

Conclusion

In view of the above, Applicants submit that the application is in condition for allowance. Reconsideration of the application and allowance of claims 1-9 and 14-22 is requested.

Respectfully submitted,

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